EXTRACRANIAL METASTASES OF A GLIOBLASTOMA MULTIFORME

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Well documented cases of extracranial metastases from primary gliomas of brain are rare. Although the literature contains reports of metastasizing gliomas, those that have been widely accepted are few. For a case to be acceptable as a true example of a metastasizing glioma, Weiss outlined the following minimal criteria:

1. The presence of a single histologically characteristic tumor of the central nervous system must have been proven.
2. The clinical history must indicate that the initial symptoms were caused by this tumor.
3. A complete autopsy must have been performed and reported in sufficient detail to rule out the possibility of any other primary site.
4. The morphology of the tumor of the central nervous system and of the distant metastases must have been identical with due allowance for differences in degrees of anaplasia.

It is believed that the following case fulfills these criteria. For the reason that a report of such a case, well documented, would be of fundamental interest to students of neoplastic diseases this presentation is made.

CASE REPORT

In December 1957 a 31-year-old white male school teacher had an attack of loss of consciousness and dizzy spells associated with involuntary twitching of the right eyelid and right shoulder. In January 1958 a second episode of unconsciousness with jerking of the head, arms and legs occurred. Electroencephalographic and pneumo-

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cosinophilic cytoplasm and nuclei containing abnormal mitotic figures were present (Fig. 1). In many areas (Fig. 2) there was pseudopalisading of elongated, somewhat spindled cells around a central area of necrosis. Vascular proliferation was very prominent with numerous large endothelial cells. The total picture was considered diagnostic of a very active glioblastoma multiforme.

Postoperative Course. The patient received a course of deep roentgen therapy (5,000 tissue roentgens) to the left frontoparietal area. His headache and seizures disappeared but he still exhibited frontal-lobe symptomatology. He was discharged from the hospital in November 1958. He was on Dilantin 100 mg. q.i.d.

When seen on April 9, 1959, the patient was teaching school and was without complaints. However, his condition changed shortly thereafter and he was readmitted to the hospital because of increasingly severe frontal headaches, anorexia, and lethargy.

2nd Admission, April 20, 1959. Neurological evaluation revealed only what were considered to be frontal-lobe symptoms—an odd affect with lack of attention, and inappropriate laughter. The hemogram was within normal limits, erythrocyte sedimentation rate was 29 mm./hr.; urinalysis, serology, blood urea nitrogen, and serum electrolytes were normal. Roentgenograms of the chest again revealed a nodular density in the right 4th interspace which was unchanged in appearance from the previous study.

Deep roentgen therapy was initiated for a second time on April 22, 1959. On April 28, 1959 he became very lethargic and semicomatose. Aspiration through one of the anterior trephine holes with removal of 35 cc. of amber-colored fluid brought about immediate improvement in his state of consciousness. Over the succeeding 12 days the cyst was re-aspirated three more times, each time with a dramatic response in his state of consciousness. Deep roentgen therapy was complete on May 25, 1959, when he had received a total of 5,000 tissue roentgens. He was discharged from the hospital on May 27, 1959. At that time he was alert, oriented, but still manifested some frontal-lobe symptoms.

Course. He was maintained on Dilantin, 100 mg. t.i.d. and meprobamate, 400 mg. q.i.d. He was able to do light work about the house, play cards, fish, etc. Then, because of pain in his left leg which gradually spread to the right leg and prevented ambulation, he was admitted to the

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**Fig. 1.** Photomicrograph of glioblastoma multiforme removed at craniotomy, showing bizarre giant cells and gemistocytic astrocytes. (X400)
hospital for the third time. The pain was located primarily in the hip and anterior area of the thighs and was not increased with coughing or sneezing. There were no headaches, seizures, nausea or vomiting, or difficulties with bowel or bladder.

3rd Admission, Aug. 3, 1959. Examination revealed point tenderness over the mid-thoracic and lumbar regions of the spine. Straight leg raising was possible to only 50 degrees bilaterally and external or internal rotation of the hips produced marked guarding of muscles. He was unable to stand because of severe pain in the lower part of the back. The only abnormal neurologic findings were the euphoria and indifferent affect noted previously.

Roentgenograms of the chest again showed the nodular density in the right 4th intercostal space, which had not changed in appearance. Roentgenograms of the thoracic spine revealed a destructive lesion involving the body of the 6th thoracic vertebra and an associated paravertebral mass. Roentgenograms of the pelvis (Fig. 3) revealed extensive rarefaction in the region of both acetabula with destruction of the cortical margin of the roof of the left acetabulum with some periosteal formation of new bone. Hemogram and urinalysis were normal. The erythrocyte sedimentation rate was 56 mm./hr. Serum calcium was 13 mg. per cent, phosphorus 3.5 mg. per cent, and acid-phosphatase 3.5 King-Armstrong units with 0.6 units being the prostatic fraction. A biopsy of the left acetabulum was obtained.

**Histological Examination.** Sections of tissue
from the acetabulum revealed an undifferentiated malignant tumor. It was very vascular and cellular, being composed of closely packed, hyperchromatic and pleomorphic cells with abundant mitotic figures. A frequent and prominent feature (Figs. 4 and 5) was pseudopalisading of elongated neoplastic cells around a centrally necrotic area, identical to that seen in the brain tumor. Vascular proliferation with actively growing endothelium was very prominent. Some multinucleated malignant giant cells with abundant eosinophilic cytoplasm were also noted. Bone spicules were scattered throughout the tumor. It was felt by several observers that the tumor in the acetabulum had histologic features very similar to those seen in the tissue obtained at the time of the craniotomy, but final opinion was deferred pending autopsy.


Autopsy. Gross Examination. The heart was normal. The right lung weighed 650 gm. and there was a sharply circumscribed whitish-yellow nodule, measuring 1.5 cm. in diameter, in the posterior basal segment. Surrounding this larger nodule there were numerous smaller circumscribed nodules in the adjacent subpleural tissue. The left lung weighed 650 gm. and contained a single subpleural nodule, measuring 3 mm. in diameter, in the lower lobe. The liver, spleen, pancreas, adrenals, kidneys and other organs of the trunk were grossly normal. A firm tan-colored mass of tumor, measuring 3×2×1 cm., was found adjacent to the 6th thoracic vertebra, with invasion and destruction of the vertebral body. A small hematoma was present in the left side of the pelvis, adjacent to the area of the surgical biopsy of the acetabulum. The brain weighed 1475 gm. The craniotomy defect was present in the left frontal region. The remaining frontal lobe was adherent to the skull and a fluid-filled cyst, 4 cm. in diameter, with a glistening lining was noted over the somewhat atrophic left frontal lobe. Firm tissue was noted extending from the left frontal lobe posteriorly into the parietal lobe. The spinal cord was not examined.

Microscopic Examination. Sections of the lung showed multiple inactive epithelioid granulomas with central necrosis. Acid-fast stains were negative for bacilli. Methenamine silver stains revealed small spherical yeast-like forms varying in size from 1 to 3 microns in diameter, diagnostic of Histoplasma capsulatum. Sections of the kid-

Fig. 4. Photomicrograph of acetabular biopsy. Note remaining spicule of bone. Tumor is composed of pseudopalisading hyperchromatic spindle cells about central fibrillar zone of necrosis. ×100)
neys showed calcium in many of the tubules.

Sections of the paravertebral mass revealed a very cellular tumor subdivided by fibrous septa and showing abundant vascular and endothelial proliferation. The tumor consisted of pleomorphic and hyperchromatic cells with many multinucleated bizarre giant forms and mitotic figures. A striking feature of the paravertebral mass was the presence of central necrotic areas surrounded by a palisaded line of fusiform or spindled hyperchromatic cells (Fig. 6). Decalcified sections of the grossly involved 6th thoracic vertebra showed tumor invading the bone and clumps of tumor within venules (Fig. 7) in the paravertebral fascia. The histologic appearance of the paravertebral mass was considered almost identical to that of the glioblastoma multiforme removed at craniotomy in 1935.

Sections of the brain revealed tumor implants in the meninges over the operative site. Sections of the brain tumor were essentially the same as described for the operative specimen.

DISCUSSION

There is general agreement that metastases of primary intracranial gliomas to extraneural locations are very rare. Virchow asserted that gliomas never metastasize outside the central nervous system. Many instances of such metastases are reported in the literature but few are documented sufficiently to be convincing. Probably the earliest generally accepted examples of extracranial metastasis of gliomas were those of Mittelbach in 1935, a case of glioblastoma multiforme of the left cerebral hemisphere with proven metastases to both lungs and hilar lymph nodes, and Nelson in 1936, a case of medulloblastoma with intradural seeding in the region of the lower part of the spinal cord and metastases to the lower four thoracic vertebrae. To these early reports must be added the cases of Köhlemeier, Abbott and Love, Brandt, Vraa-Jensen, Sikl, Cross and Cooper, James and Pagel, Sherbaniuk and Shnitka, Maass, Perry, Wen and Barrows, Thiry et al., Giok and v. d. Schoot, Rubinstein, and Ley et al.

There has been but one other reported case (Wolf et al.) of a glioblastoma multiforme...
Fig. 6. Photomicrograph of tissue from paravertebral mass showing gemistocytic astrocytes and zone of pseudopalisading spindle cells about central zone of fibrillar necrosis. (X400)

Fig. 7. Photomicrograph of another area in paravertebral mass with vascular invasion by nests of glioma. (X400)
metastasizing to bone, and in this case, a ventriculopleural shunt was performed because of obstruction of the cerebrospinal fluid circulation. At necropsy, 8½ months following the shunting procedure, it was found that the shunt had served not only as a conduit for cerebrospinal fluid, but also for tumor cells. Metastases from the glioblastoma were noted in the pleura, and bone marrow of the ribs, sternum and vertebra. Obviously this case presents a situation entirely different from that presented in this report. Our case, to the best of our knowledge, is the only reported case of “spontaneous” metastasis of a glioblastoma multiforme to bone. The premortem knowledge of a destructive lesion in the acetabulum and in the 6th thoracic vertebra alerted us to the possibility of a metastasizing glioma. The absence of any visceral tumor, primary or metastatic, makes unlikely the possibility of a small primary tumor in the lung, pancreas, or any other organ with predilection for cryptic primary site of origin. The possibility of a primary bone tumor in the acetabulum was considered but ruled out because of the bilaterality, and the lack of radiological or histological resemblance to any primary tumor of bone.

Weiss' criteria for metastasizing gliomas are fulfilled. The primary intracranial neoplasm was a classical glioblastoma multiforme with pleomorphism of cells, necrosis, hyperchromaticity, and vascular proliferation. Symptoms of the tumor began in December 1957, and symptoms of bony involvement in August 1959, 1 month before death. With the possibility that a metastasizing glioma was present a thorough necropsy was performed to rule out any other primary site. Finally, definite histological resemblance of the primary and metastatic tumor is agreed upon by several observers.

The apparent ability of gliomas to invade blood vessels intracranially is widely recognized. The extraordinary infrequency of this event is illustrated by the fact that only four authors—Köhlmeier, Mittelbach, Weiss, and Russell (cited by Rubinstein)—have described a gliomatous penetration of veins or sinuses intracranially. Then how does hematogenous dissemination take place and is it really hematogenous? The one feature common to all reported cases of metastasizing glioma is surgical intervention. During the course of operation, many venous channels are opened. Abbott and Love felt that the negative intraluminal pressure present in these veins favored aspiration of neoplastic cells into their lumina with widespread dissemination therefore possible. This concept of venous implantation at the time of operation is quoted widely as a means of hematogenous spread of gliomas.

Another factor contributing to the rarity of gliogenous metastases is the absence of lymphatic channels within the brain. Surgery, by bringing intracranial tumor in contact with extracranial lymphatic channels, favors lymphatic spread of gliomas. Cases have been reported of local recurrences in the scalp with secondary involvement of cervical and hilar lymph nodes following craniotomy for the removal of gliomas. Lastly, surgery may be incriminated for prolonging the period of survival. Either with or without surgical intervention, the majority of cases of malignant glioma of the central nervous system follow a very rapid fatal course. When surgery does prolong survival after removal of the glioma, it is reasonable to believe that this would enhance the likelihood of metastases. It is believed that surgery plus deep roentgen therapy certainly were instrumental in increasing the survival period of the patient presented in this report.

Winkelman and others have advanced the supposition that one reason for the paucity of extraneural gliogenous metastasis is that these tissues constitute a poor medium for growth of gliomas. The work of Zimmerman refutes this proposal. He has shown that carcinogenically-induced gliomas in mice thrive when transplanted artificially to extracranial locations. Further, he has demonstrated that homogenates of experimental gliomas injected intravenously in mice will result in widespread visceral deposits. This experience in mice probably would not be reproducible in man, and this is supported by
the fact that Greene was unable to implant human glioblastoma multiforme in animal issues other than the brain or eye.

Recently, Grace et al. have successfully transplanted subcutaneous autografts in 2 of 6 patients with glioblastoma multiforme. The neoplastic proliferation in the subcutaneous tissue was typical of glioblastoma multiforme. They have postulated that the presence of delayed hypersensitivity to antigens of tumors of the central nervous system may have played a role in determining the success or failure of the autografts.

Roentgen-ray therapy has been another relatively common factor noted in most of the reported cases of gliogenous metastases. Zimmerman demonstrated experimentally that alteration of the morphologic appearance and acceleration of the rate of growth of gliomas could be brought about by the use of deep roentgen irradiation; however, using irradiation alone, he was unable to produce a glioma or cause a metastatic spread of an intracranial tumor.

Another etiologic factor alluded to by Maass was the possibility of heterotopic glial rests in the dura mater, leptomeninges, or the mesodermal tissue outside the central nervous system. The frequency of metastases with dural tumors certainly is greater than with glial tumors. There is no proof that this was a factor in the case presented here. It is believed that surgical intervention and the deep roentgen therapy with prolonged survival (21 months) have played a role in permitting the extracranial metastases to occur and survive in this patient with a glioblastoma multiforme.

SUMMARY
1. A case of glioblastoma multiforme, fulfilling Weiss criteria, metastasizing to the 6th thoracic vertebra and acetabula, is reported.
2. Surgical intervention and possibly deep roentgen therapy with prolonged survival are offered as an explanation for the extracranial metastases.

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